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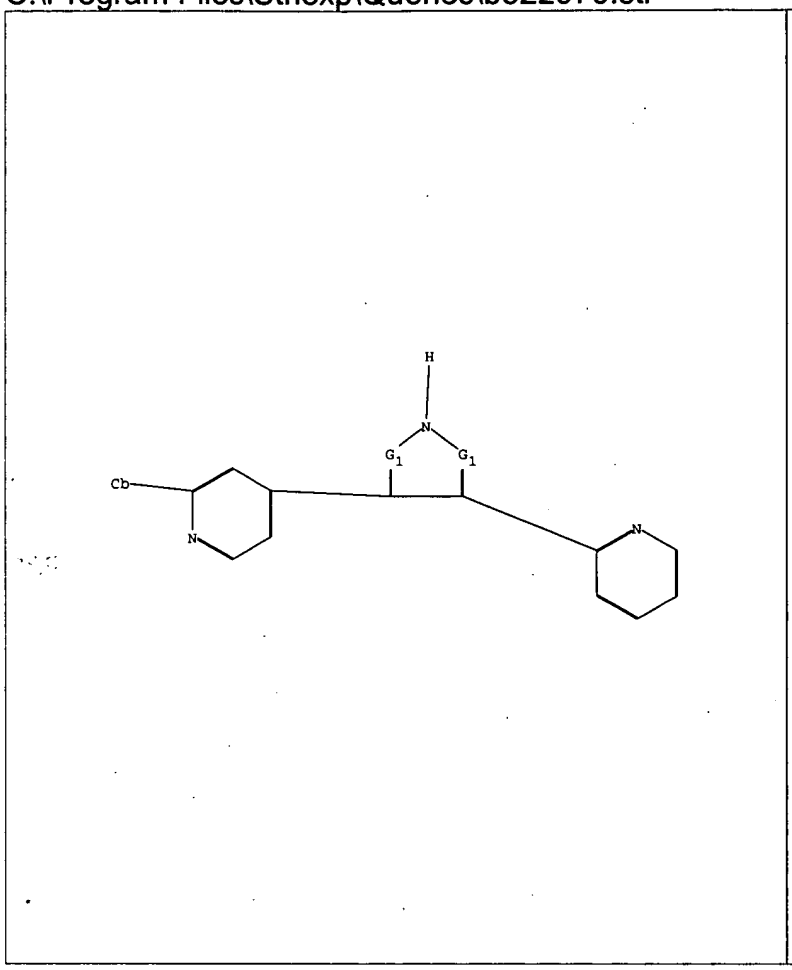

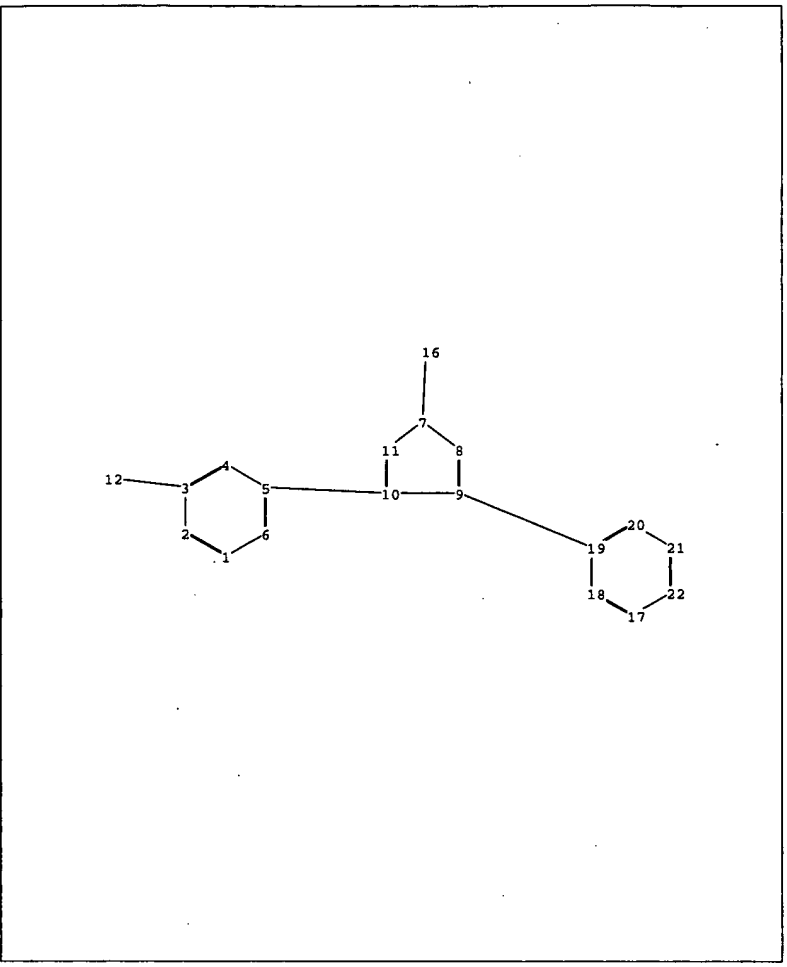

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12 16
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 17 18 19 20 21 22
chain bonds :
3-12 5-10 7-16 9-19
ring bonds :
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exact/norm bonds :
3-12 5-10 7-8 7-11 7-16 8-9 9-10 9-19 10-11
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 17-18 17-22 18-19 19-20 20-21 21-22
isolated ring systems :
containing 1 : 7 :

G1:C,N

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom
16:CLASS 17:Atom 18:Atom 19:CLASS 20:Atom 21:Atom 22:Atom
Generic attributes :
12:
Saturation : Unsaturated

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L3           43 S L1 FULL

      FILE 'STNGUIDE' ENTERED AT 13:19:32 ON 24 OCT 2006

      FILE 'REGISTRY' ENTERED AT 13:20:39 ON 24 OCT 2006
L4              STRUCTURE UPLOADED
L5            7 S L4 SAM
L6           88 S L4 FULL

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L7            5 S L6
L8            1 S L7 AND PD<JULY 2003
file reg

=> Uploading C:\Program Files\Stnexp\Queries\b522970.str
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12  16
ring nodes :
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chain bonds :
3-12  5-10  7-16  9-19
ring bonds :
1-2  1-6  2-3  3-4  4-5  5-6  7-8  7-11  8-9  9-10  10-11  17-18  17-22  18-19  19-
20  20-21  21-22
exact/norm bonds :
3-12  5-10  7-8  7-11  7-16  8-9  9-10  9-19  10-11
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6  17-18  17-22  18-19  19-20  20-21  21-22
isolated ring systems :
containing 1 : 7 :


G1:C,N

Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:Atom  12:Atom  16:CLASS  17:Atom  18:Atom  19:CLASS  20:Atom  21:Atom  22:Atom
Generic attributes :
12:
Saturation              : Unsaturated




L4      STRUCTURE UPLOADED

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L4 HAS NO ANSWERS
L4              STR

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

Structure attributes must be viewed using STN Express query preparation.


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L5            7 SEA SSS SAM L4

=> s l4 full
L6           88 SEA SSS FUL L4

=> file caplus


=> s l6
L7            5 L6

=> s l7 and pd<july 2003
      23677239 PD<JULY 2003
                (PD<20030700)
L8            1 L7 AND PD<JULY 2003

=> dis bib abs

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AN   2002:658110  CAPLUS Full-text
DN   137:201305
TI   Pyridinyl-substituted pyrazole derivatives useful against TGF-β
     overexpression, and their preparation and use
IN   Gellibert, Francoise Jeanne; Mathews, Neil
PA   Glaxo Group Limited, UK
SO   PCT Int. Appl., 62 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
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             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
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         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
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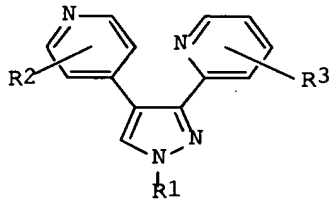

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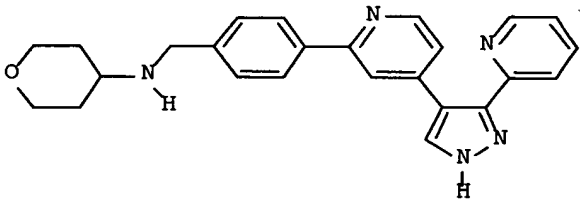

II

AB Therapeutically active pyrazole derivs. of formula I are disclosed, as well as processes for their preparation, their use in therapy [particularly in the treatment or prophylaxis of disorders characterized by overexpression of transforming growth factor β (TGF-β)], and pharmaceutical compns. for use in such therapy. In formula I, R1 is selected from H, C1-4 alkyl or CH2CONR4R5, where R4 is selected from H or C1-4 alkyl and R5 is C1-4 alkyl; R2 is selected from Ph, furanyl, or thienyl, wherein the Ph may be further substituted by one or more substituents, which may be the same or different, selected from halo (such as F, Cl, Br), cyano, CF3, OCF3, C1-4 alkyl, OR6, O(CH2)nXR6R7, O(CH2)nOR6, O(CH2)nCOR6, O(CH2)n-C2-6-alkenyl, O(CH2)n-C2-6-alkynyl, (CH2)nNR6R7, CONR6R7, NHCOR6, and NR6R7, where n is 1 to 6, and X is C, N, or S, and wherein the furanyl and thienyl may be further substituted by one or more substituents, which may be the same or different, selected from halo, cyano, CF3, OH, OCF3, C1-4 alkyl, and C1-4 alkoxy. Furthermore, R6 and R7 which may be the same or different, are selected from H, C1-6 alkyl, cycloalkyl, cycloalkyl-C1-6-alkyl, aryl, aryl-C1-6-alkyl, heteroaryl, heteroaryl-C1-6-alkyl, heterocyclyl, heterocyclyl-C1-6-alkyl, C1-4-alkoxy-C1-6-alkyl, hydroxy-C1-6-alkyl, (CH2)nNR8R9; or R6R7 together with the atom to which they are attached form a 3- to 7-membered saturated or unsatd. ring which may contain one or more heteroatoms selected from N, S, or O, and wherein the ring may be further substituted by one or more substituents selected from halo, cyano, CF3, OH, OCF3, C1-4 alkyl, C1-4 alkoxy and NR8R9; R8 and R9 which may be the same or different are selected from H or C1-6 alkyl, wherein the C1-6 alkyl may be further substituted by one or more substituents selected from halo, cyano, CF3, and OH; R3 is selected from H, halo, cyano, CF3, C1-4 alkyl, and C1-4 alkoxy. Salts and solvates of I are included as well. I are TGF-β inhibitors which act at the TGF-β type I (Alk5) receptor level, and thereby inhibit phosphorylation of the Smad-2 or Smad-3 proteins. Projected uses include treatment or prophylaxis of diseases such as fibrosis (especially liver or kidney), cancer development, abnormal bone function, inflammatory disorders, and scarring. The compds. are particularly suited to treatment of fibrosis and related conditions. Prepns. of 47 compds.

and various intermediates are given. For instance, 2-bromo-4-methylpyridine was deprotonated and condensed with Et picolinate to give 2-(2-bromopyridin-4-yl)-1-(pyridin-2-yl)ethanone. Cyclocondensation of this ketone with DMF di-Me acetal and hydrazine gave the corresponding pyrazole, which was protected by N-tritylation and arylated at bromine using 4-formylphenylboronic acid under Pd(0) catalysis. The resultant aldehyde was reductively aminated by 4-aminotetrahydropyran and NaBH(OAc)3 to give title compound II. All 47 compds. I inhibited TGF-β signaling in vitro with IC50 values of 5 μM or below, and inhibited the kinase Alk5 receptor (cloned, expressed in baculovirus/Sf9 cells) with IC50 values of 1 μM or less.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN

IT 452342-37-9P, 2-Phenyl-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-38-0P, 2-[4-(Trifluoromethyl)phenyl]-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-39-1P, 2-(4-Methoxyphenyl)-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-40-4P, 2-(4-Fluorophenyl)-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-41-5P, 2-(4-Chlorophenyl)-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-43-7P, 2-[4-(Trifluoromethoxy)phenyl]-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-44-8P, 2-(4-Methylphenyl)-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-45-9P, 2-(4-Ethylphenyl)-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-48-2P, 2-[4-[2-(Pyrrolidin-1-yl)ethoxy]phenyl]-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-50-6P, 3-[[4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzyl]amino]propanenitrile 452342-51-7P, 4-[4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]morpholine 452342-52-8P, 2-[4-[(1-Methyl-1H-imidazol-4-yl)methoxy]phenyl]-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-53-9P, 2-[4-[(1-Methyl-1H-imidazol-2-yl)methoxy]phenyl]-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-54-0P, 2-[4-[(3-Methyl-3H-imidazol-4-yl)methoxy]phenyl]-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-55-1P, 2-[4-[2-(1H-Imidazol-1-yl)ethoxy]phenyl]-4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridine 452342-56-2P, [4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzyl](tetrahydropyran-4-yl)amine 452342-57-3P, 4-[4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzyl]morpholine hydrochloride 452342-58-4P, (Pyridin-3-ylmethyl)[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzyl]amine 452342-59-5P, 2-(Piperidin-1-yl)-N-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]acetamide 452342-60-8P, 2-(Pyrrolidin-1-yl)-N-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]acetamide 452342-61-9P, 2-(Morpholin-4-yl)-N-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]acetamide 452342-62-0P, 2-(4-Methylpiperazin-1-yl)-N-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]acetamide 452342-63-1P, 3-(Piperidin-1-yl)-N-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]propionamide hydrochloride 452342-64-2P, 3-(Morpholin-4-yl)-N-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]propionamide 452342-65-3P, 3-(4-Methylpiperazin-1-yl)-N-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]propionamide 452342-67-5P, 4-[4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]-N-(tetrahydropyran-4-yl)benzamide 452342-69-7P, N-[(1-Ethylpyrrolidin-2-yl)methyl]-4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]benzamide 452342-71-1P, 1-Ethyl-4-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl]piperazine 452342-73-3P, N-Methyl-[4-[4-[3-(pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl]phenyl](tetrahydropyran-4-yl)amine 452342-75-5P,

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RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate)

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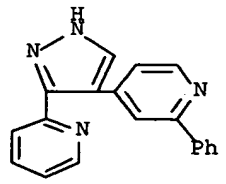

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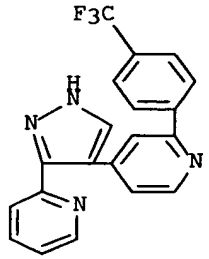

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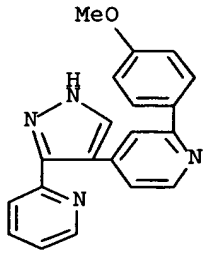

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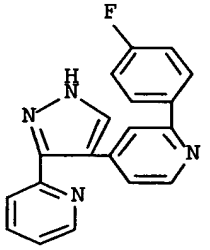

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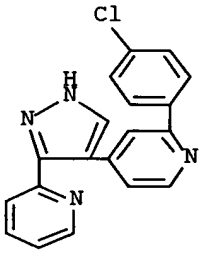

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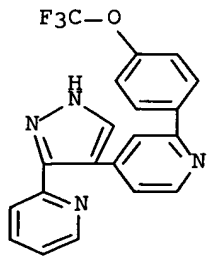

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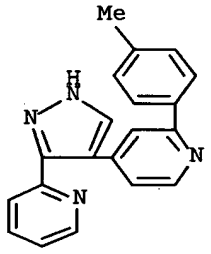

RN 452342-45-9 CAPLUS
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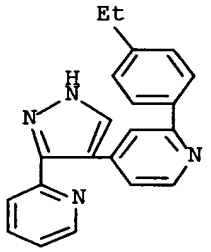

RN 452342-48-2 CAPLUS
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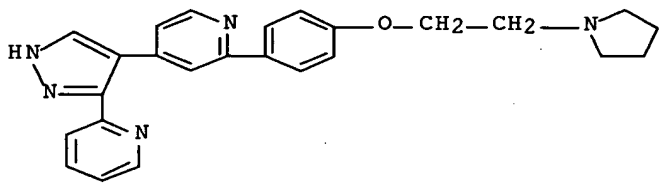

RN 452342-50-6 CAPLUS

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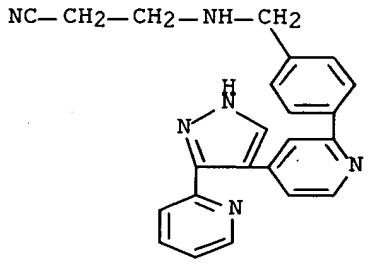

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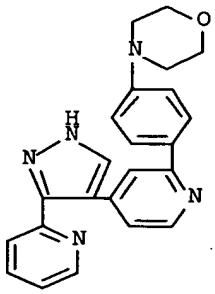
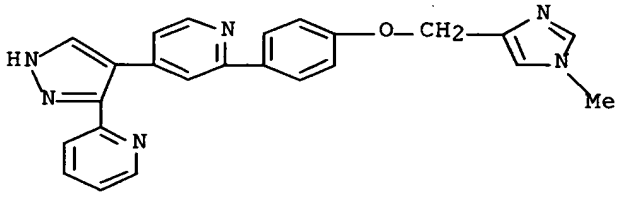
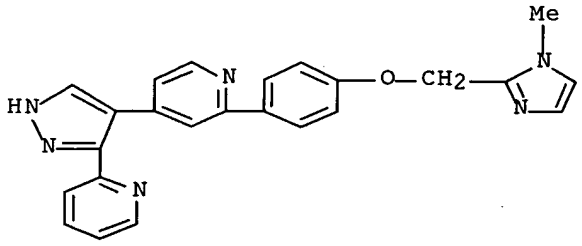


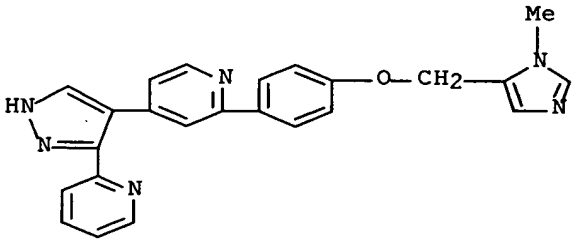
RN 452342-52-8 CAPLUS
CN Pyridine, 2-[4-[(1-methyl-1H-imidazol-4-yl)methoxy]phenyl]-4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]- (9CI) (CA INDEX NAME)



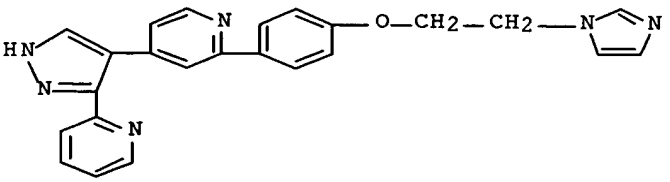
RN 452342-53-9 CAPLUS
CN Pyridine, 2-[4-[(1-methyl-1H-imidazol-2-yl)methoxy]phenyl]-4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]- (9CI) (CA INDEX NAME)



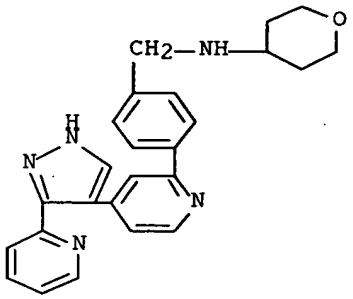
RN 452342-54-0 CAPLUS
CN Pyridine, 2-[4-[(1-methyl-1H-imidazol-5-yl)methoxy]phenyl]-4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]- (9CI) (CA INDEX NAME)



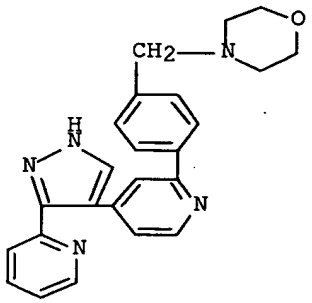
RN 452342-55-1 CAPLUS
CN Pyridine, 2-[4-[2-(1H-imidazol-1-yl)ethoxy]phenyl]-4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]- (9CI) (CA INDEX NAME)



RN 452342-56-2 CAPLUS
CN 2H-Pyran-4-amine, tetrahydro-N-[[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

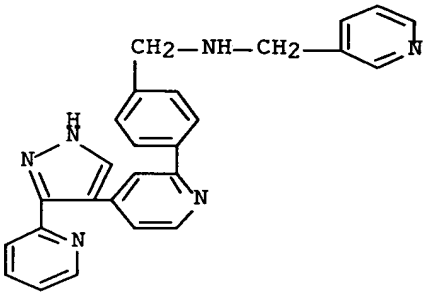


RN 452342-57-3 CAPLUS
CN Morpholine, 4-[[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]methyl]-, hydrochloride (9CI) (CA INDEX NAME)



●x HCl

RN 452342-58-4 CAPLUS
CN 3-Pyridinemethanamine, N-[[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 452342-59-5 CAPLUS
CN 1-Piperidineacetamide, N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)

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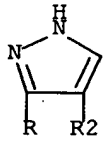

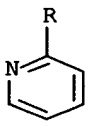

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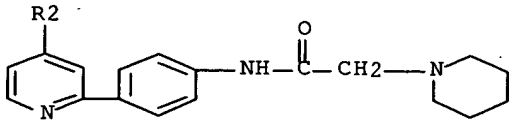
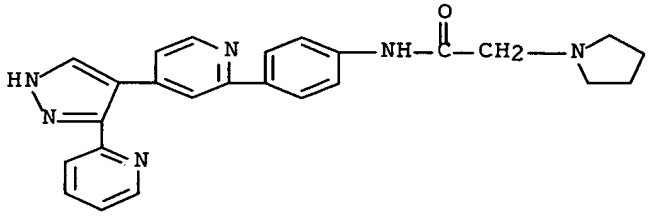


RN 452342-60-8 CAPLUS
CN 1-Pyrrolidineacetamide, N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)



RN 452342-61-9 CAPLUS
CN 4-Morpholineacetamide, N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)

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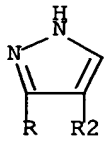

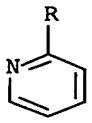

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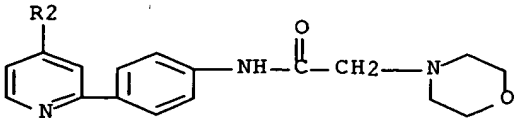

RN 452342-62-0 CAPLUS
CN 1-Piperazineacetamide, 4-methyl-N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)

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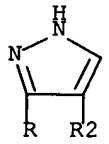

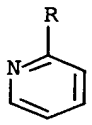

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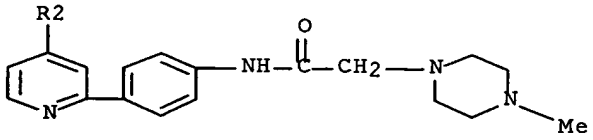

RN 452342-63-1 CAPLUS
CN 1-Piperidinepropanamide, N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]-, hydrochloride (9CI) (CA INDEX NAME)

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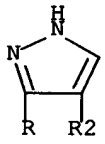

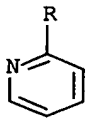

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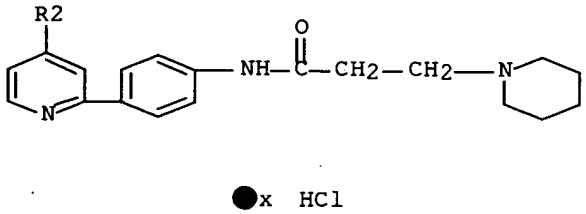

RN 452342-64-2 CAPLUS

CN 4-Morpholinepropanamide, N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)

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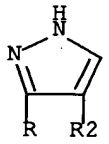

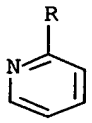

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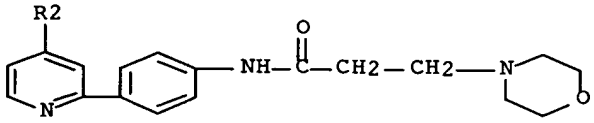

RN 452342-65-3 CAPLUS

CN 1-Piperazinepropanamide, 4-methyl-N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)

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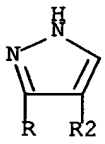

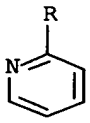

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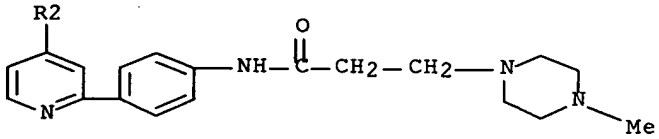
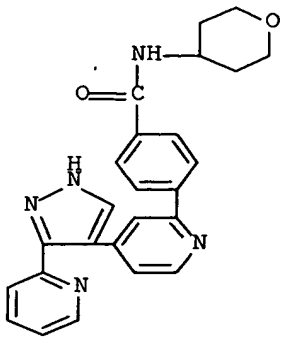


RN 452342-67-5 CAPLUS

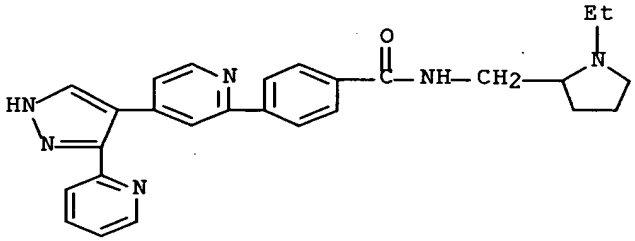
CN Benzamide, 4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]-N-

(tetrahydro-2H-pyran-4-yl)- (9CI) (CA INDEX NAME)



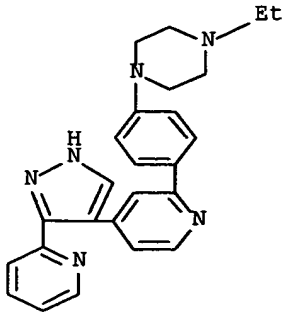
RN 452342-69-7 CAPLUS

CN Benzamide, N-[(1-ethyl-2-pyrrolidinyl)methyl]-4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]- (9CI) (CA INDEX NAME)



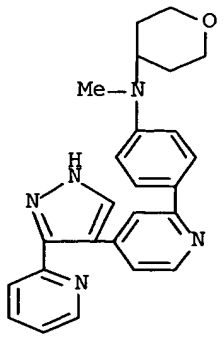
RN 452342-71-1 CAPLUS

CN Piperazine, 1-ethyl-4-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)

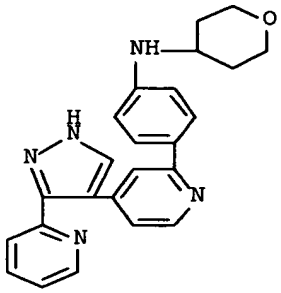


RN 452342-73-3 CAPLUS

CN 2H-Pyran-4-amine, tetrahydro-N-methyl-N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)



RN 452342-75-5 CAPLUS
CN 2H-Pyran-4-amine, tetrahydro-N-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)



RN 452342-77-7 CAPLUS
CN 2H-Pyran-4-amine, tetrahydro-N-methyl-N-[[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)

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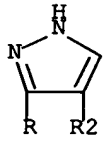

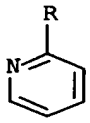

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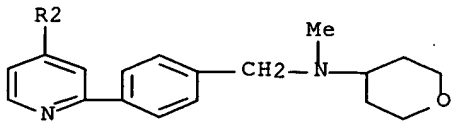
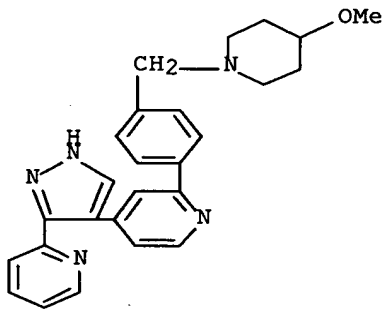
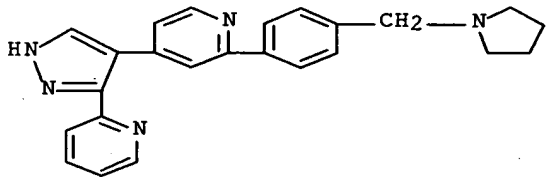


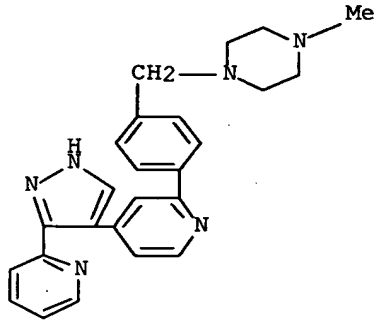
RN 452342-79-9 CAPLUS
CN Pyridine, 2-[4-[(4-methoxy-1-piperidinyl)methyl]phenyl]-4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]- (9CI) (CA INDEX NAME)



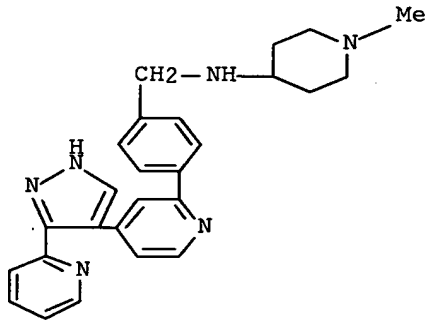
RN 452342-81-3 CAPLUS
CN Pyridine, 4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-[4-(1-pyrrolidinylmethyl)phenyl]- (9CI) (CA INDEX NAME)



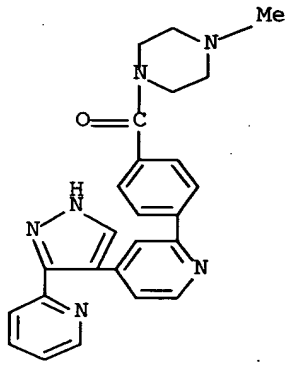
RN 452342-83-5 CAPLUS
CN Piperazine, 1-methyl-4-[[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



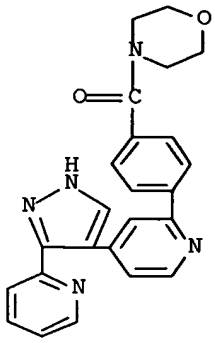
RN 452342-85-7 CAPLUS
CN 4-Piperidinamine, 1-methyl-N-[[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



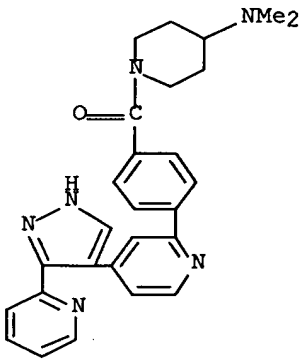
RN 452342-87-9 CAPLUS
CN Piperazine, 1-methyl-4-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]benzoyl]- (9CI) (CA INDEX NAME)



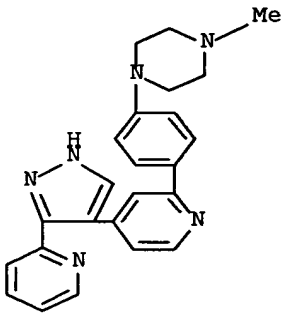
RN 452342-89-1 CAPLUS
CN Morpholine, 4-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]benzoyl]- (9CI) (CA INDEX NAME)



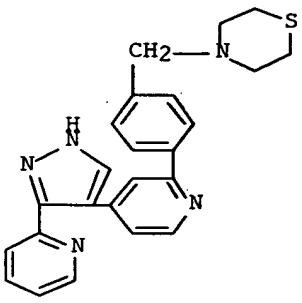
RN 452342-90-4 CAPLUS
CN 4-Piperidinamine, N,N-dimethyl-1-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]benzoyl]- (9CI) (CA INDEX NAME)



RN 452342-92-6 CAPLUS
CN Piperazine, 1-methyl-4-[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]- (9CI) (CA INDEX NAME)

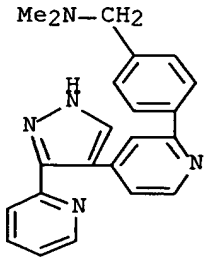


RN 452342-93-7 CAPLUS
CN Thiomorpholine, 4-[[4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]phenyl]methyl]- (9CI) (CA INDEX NAME)



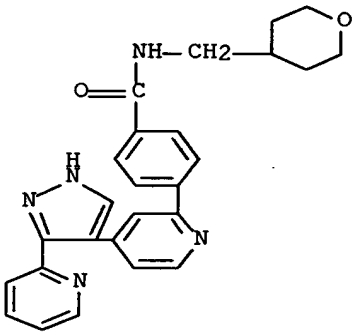
RN 452342-94-8 CAPLUS

CN Benzenemethanamine, N,N-dimethyl-4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]- (9CI) (CA INDEX NAME)



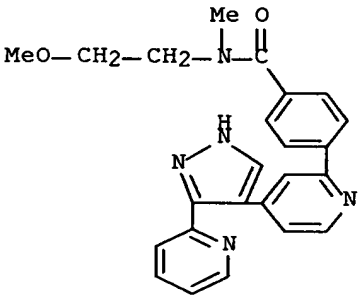
RN 452342-95-9 CAPLUS

CN Benzamide, 4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]-N-[(tetrahydro-2H-pyran-4-yl)methyl]- (9CI) (CA INDEX NAME)



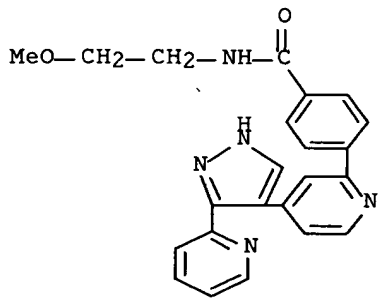
RN 452342-96-0 CAPLUS

CN Benzamide, N-(2-methoxyethyl)-N-methyl-4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]- (9CI) (CA INDEX NAME)

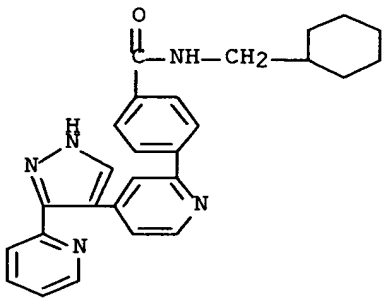


RN 452342-97-1 CAPLUS

CN Benzamide, N-(2-methoxyethyl)-4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]- (9CI) (CA INDEX NAME)



RN 452342-98-2 CAPLUS
CN Benzamide, N-(cyclohexylmethyl)-4-[4-[3-(2-pyridinyl)-1H-pyrazol-4-yl]-2-pyridinyl]- (9CI) (CA INDEX NAME)



=> s l7 not l8
L9 4 L7 NOT L8

=> dis 1-4 bib abs

L9 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2006:237133 CAPLUS Full-text
DN 144:460293
TI Discovery of 4-{4-[3-(Pyridin-2-yl)-1H-pyrazol-4-yl]pyridin-2-yl}-N-(tetrahydro-2H- pyran-4-yl)benzamide (GW788388): A Potent, Selective, and Orally Active Transforming Growth Factor-β Type I Receptor Inhibitor
AU Gellibert, Francoise; de Gouville, Anne-Charlotte; Woolven, James; Mathews, Neil; Nguyen, Van-Loc; Bertho-Ruault, Cecile; Patikis, Angela; Grygielko, Eugene T.; Laping, Nicholas J.; Huet, Stephane
CS Department of Medicinal Chemistry and Biology, GlaxoSmithKline, Les Ulis, 91951, Fr.
SO Journal of Medicinal Chemistry (2006), 49(7), 2210-2221
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 144:460293
AB Inhibitors of transforming growth factor β (TGF-β) type I receptor (ALK5) offer a novel approach for the treatment of fibrotic diseases such as renal, hepatic, and pulmonary fibrosis. The optimization of a novel phenylpyridine

pyrazole series (1a) led to the identification of potent, selective, and orally active ALK5 inhibitors. The cellular potency and pharmacokinetics profiles of these derivs. were improved and several compds. presented antifibrotic activity when orally administered to rats in an acute liver model of dimethylnitrosamine- (DMN-) induced expression of collagen IA1 mRNA, a major gene contributing to excessive extra cellular matrix deposit. One of the most potent ALK5 inhibitors identified in this chemical series, compound 13d (GW788388), reduced the expression of collagen IA1 by 80% at a dose of 1 mg/kg twice a day (b.i.d.). This compound significantly reduced the expression of collagen IA1 mRNA when administered orally at 10 mg/kg once a day (u.i.d.) in a model of puromycin aminonucleoside-induced renal fibrosis.

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:420278 CAPLUS Full-text
DN 143:126677
TI Inhibition of TGF-β signaling by an ALK5 inhibitor protects rats from dimethylnitrosamine-induced liver fibrosis
AU de Gouville, Anne-Charlotte; Boullay, Valerie; Krysa, Gael; Pilot, Julia; Brusq, Jean-Marie; Loriolle, Florence; Gauthier, Jean-Michel; Papworth, Stephen A.; Laroze, Alain; Gellibert, Francoise; Huet, Stephane
CS Biology Department, GlaxoSmithKline, Les Ulis, 91951, Fr.
SO British Journal of Pharmacology (2005), 145(2), 166-177
CODEN: BJPCBM; ISSN: 0007-1188
PB Nature Publishing Group
DT Journal
LA English
AB Chronic liver disease is characterized by an exacerbated accumulation of matrix, causing progressive fibrosis, which may lead to cirrhosis. Transforming growth factor beta (TGF-β), a well-known profibrotic cytokine, transduces its signal through the ALK5 ser/thr kinase receptor, and increases transcription of different genes including PAI-1 and collagens. The identification of GW6604 (2-phenyl-4-(3-pyridin-2-yl-1H- pyrazol-4-yl)pyridine), an ALK5 inhibitor, allowed us to evaluate the therapeutic potential of inhibiting TGF-β pathway in different models of liver disease. A cellular assay was used to identify GW6604 as a TGF-β signaling pathway inhibitor. This ALK5 inhibitor was then tested in a model of liver hepatectomy in TGF-β-overexpressing transgenic mice, in an acute model of liver disease and in a chronic model of dimethylnitrosamine (DMN)-induced liver fibrosis. In vitro, GW6604 inhibited autophosphorylation of ALK5 with an IC50 of 140 nM and in a cellular assay inhibited TGF-β-induced transcription of PAI-1 (IC50: 500 nM). In vivo, GW6604 (40 mg kg-1 p.o.) increased liver regeneration in TGF-β-overexpressing mice, which had undergone partial hepatectomy. In an acute model of liver disease, GW6604 reduced by 80% the expression of collagen IA1. In a chronic model of DMN-induced fibrosis where DMN was administered for 6 wk and GW6604 dosed for the last 3 wk (80 mg kg-1 p.o., b.i.d.), mortality was prevented and DMN-induced elevations of mRNA encoding for collagen IA1, IA2, III, TIMP-1 and TGF-β were reduced by 50-75%. Inhibition of matrix genes overexpression was accompanied by reduced matrix deposition and reduction in liver function deterioration, as assessed by bilirubin and liver enzyme levels. Our results suggest that inhibition of ALK5 could be an attractive new approach to treatment of liver fibrotic diseases by both preventing matrix deposition and promoting hepatocyte regeneration.

RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2004:162684 CAPLUS Full-text
DN 140:199324
TI Preparation of (pyridyl)(phenylpyridyl)pyrazoles as inhibitors of the transforming growth factor β
IN Gellibert, Francoise Jeanne
PA Smithkline Beecham Corporation, USA
SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004016606	A1	20040226	WO 2003-EP8449	20030729
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003255333	A1	20040303	AU 2003-255333	20030729
	EP 1554268	A1	20050720	EP 2003-787752	20030729
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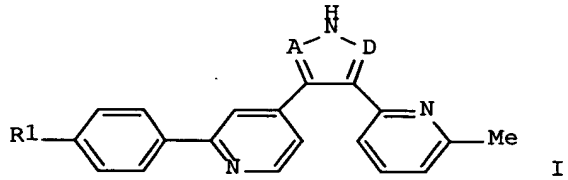
	JP 2005539026	T2	20051222	JP 2004-528450	20030729
	US 2006058329	A1	20060316	US 2005-522970	20050131
PRAI	GB 2002-17786	A	20020731		
	WO 2003-EP8449	W	20030729		

OS MARPAT 140:199324
GI



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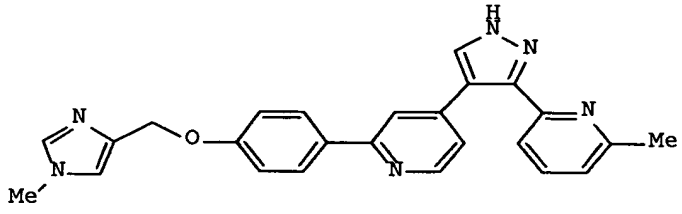

II

AB Title compds. I [wherein either A = CR2 and D = N or A = N and D = CR2; R1 = H, (perfluoro)alkyl, alkenyl, (perfluoro)alkoxy, halo, cyano, NR3R4, (CH2)nNR3R4, O(CH2)nOR5, O(CH2)nNR3R4, O(CH2)n-Het, CONR3R4, CO(CH2)nNR3R4, SO2R5, SO2NR3R4, NR3SO2R5, NR3COR5, NR3CO(CH2)nNR3R4, Het, or O(CH2)nCONR3R4; R2 = H or alkyl; R3 and R4 = independently H, (alkoxy)alkyl, or Het; or NR3R4

= (un)substituted heterocyclyl; R5 = H or alkyl; Het = (un)substituted 5- or 6-membered C-linked heterocyclyl; n = 1-4; or pharmaceutically acceptable salts, solvates, or derivs. thereof] were prepared as inhibitors of the transforming growth factor β (TGF-β) signaling pathway, in particular, the phosphorylation of smad2 or smad3 by the TGF-β type I or activin-like kinase (ALK) 5 receptor. For example, reaction of 4-[4-[3-(6-methylpyridin-2-yl)-1-trityl-1H-pyrazol-4-yl]pyridin-2-yl]phenol with 1-methyl-4-chloromethylimidazole•HCl (preparation of starting materials given) in the presence of NaH in CH2Cl2 provided the trityl intermediate, which was deprotected using HCl in MeOH to give II (37%). The latter inhibited TGF-β signaling in HepG2 cells stably transfected with the PAI-1 promotor linked to a luciferase reporter gene with an IC50 value of 34 nM. II also modulated ALK5 receptor activity with an IC50 value of 5 nM. Thus, I and their pharmaceutical compns. are useful for the treatment of disorders mediated by the ALK5 receptor, such as kidney fibrosis (no data).

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:120851 CAPLUS Full-text
DN 140:181331
TI Preparation of 2-phenylpyridin-4-yl heterocycles as selective activin-like kinase-5 inhibitors useful against fibrosis and other disorders
IN Dodic, Nerina; Gellibert, Francoise Jeanne
PA Smithkline Beecham Corporation, USA
SO PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004013135	A1	20040212	WO 2003-EP8496	20030729
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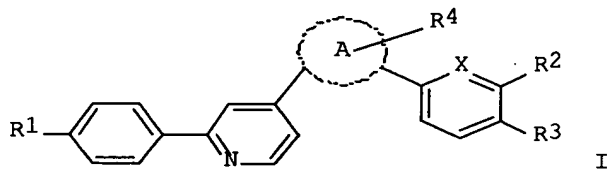
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2003260345	A1	20040223	AU 2003-260345	20030729
	EP 1539748	A1	20050615	EP 2003-766385	20030729
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	JP 2005539000	T2	20051222	JP 2004-525405	20030729
	US 2005245520	A1	20051103	US 2005-522969	20050131
PRAI	GB 2002-17751	A	20020731		
	GB 2003-14698	A	20030624		
	WO 2003-EP8496	W	20030729		

OS MARPAT 140:181331
GI



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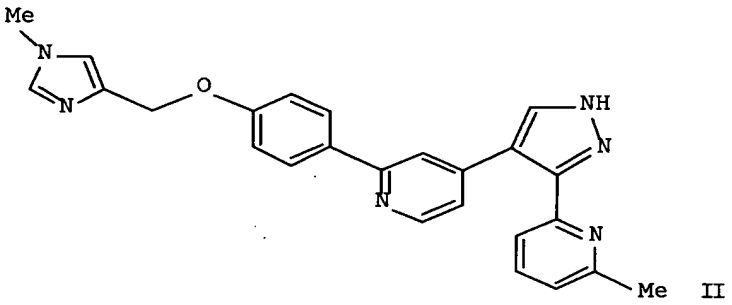

II

AB This invention relates to novel 2-phenylpyridin-4-yl heterocycles (shown as I; variables defined below; e.g. II) that are inhibitors of the transforming growth factor, ('TGF')-β signaling pathway, in particular, the phosphorylation of Smad-2 or Smad-3 by the TGF-β type I or activin-like kinase ('ALK')-5 receptor, methods for their preparation and their use in medicine, specifically in the treatment and prevention of a disease state mediated by this pathway, e.g. fibrosis (no data). All examples of I show ALK-5 receptor modulator activity (having IC50 values at 0.4-275 nM) and TGF-β cellular activity (having IC50 values at 0.001-10 μM). 4-[4-[4-[2-tert-Butyl-5-(6-methylpyridin-2-yl)-1H- imidazol-4-yl]pyridin-2-yl]phenyl]morpholine showed an ALK-5 receptor modulator activity of 34 nM and TGF-β cellular activity of 183 nM. N-(tetrahydropyran-4-yl)-4-[4-[2-isopropyl-5-(6-methylpyridin-2-yl)-1H-imidazol-4-yl]pyridin-2-yl]benzamide showed an ALK-5 receptor modulator activity of 25 nM and TGF-β cellular activity of <14 nM. Although the methods of preparation are not claimed, >150 example prepns. of I and .apprx.130 example prepns. of intermediates are included. For example, II was prepared in 37% yield by reacting 4-[4-[3-(6-methylpyridin-2-yl)-1- trityl-1H-pyrazol-4-yl]pyridin-2-yl]phenol and NaH in DMF with 1-methyl-4-hydroxymethylimidazole followed by removal of the trityl group using HCl in MeOH; details are also given for preparation of the reactants. For I: A is furan, dioxolane, thiophene, pyrrole, imidazole, pyrrolidine, pyran, pyridine, pyrimidine, morpholine, piperidine, oxazole, isoxazole, oxazoline, oxazolidine, thiazole, isothiazole, thiadiazole, benzofuran, indole, isoindole, indazole, imidazopyridine, quinazoline, quinoline, isoquinoline, pyrazole or triazole; X is N or CH; R1 is H, C1-6alkyl, C1-6alkenyl, C1-6alkoxy, halo, cyano, perfluoro C1-6alkyl, perfluoroC1-6alkoxy, -NR5R6, -(CH2)nNR5R6, -O(CH2)nOR7, -O(CH2)n-Het, -O(CH2)nNR5R6, -CONR5R6, -CO(CH2)nNR5R6, -SO2R7, -SO2NR5R6, -NR5SO2R7, -NR5COR7, -O(CH2)nCONR5R6, -NR5CO(CH2)nNR5R6 or -C(O)R7; R2 is H, C1-6alkyl, halo, cyano or perfluoroC1-6alkyl; R3 is H or halo; R4 is H, halo, Ph, C1-6alkyl or -NR5R6; addnl. details including provisos are given in the claims.

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COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION

FULL ESTIMATED COST	18.94	372.59
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.75	-3.75

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